



## DAIRY FOODS & CANCER PREVENTION

### SUMMARY

Cancer is the second most common cause of death in the U.S. Both genetic and environmental factors influence cancer risk. Awareness of relationships between diet, specific foods including dairy products, and cancer has been heightened by the recent release of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)'s Second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective*. This Digest reviews some of the findings in this report, as well as new research related to the role of dairy foods and dairy food nutrients in colorectal, breast, and prostate cancers.

Experimental animal, *in vitro*, epidemiological, and clinical studies suggest a protective role for dairy foods and dairy food nutrients such as calcium and vitamin D in colorectal cancer. Based on reasonably consistent findings from epidemiological (cohort) studies, strong evidence from dietary calcium studies, and evidence for plausible mechanisms, the WCRF/AICR second Expert Report concludes that "milk probably protects against colorectal cancer." Additional support for a protective effect of calcium, vitamin D, and dairy products comes from some recent studies not included in the WCRF/AICR report.

Epidemiological studies have shown either no or a moderately lower risk of developing breast cancer with increased intake of dairy foods, calcium, or vitamin D. Some of the inconsistent findings may be explained in part by the menopausal status of study participants and the stage of cancer. The apparent protective effect of calcium and vitamin D may be greater for

premenopausal than postmenopausal women and for more advanced/aggressive than less advanced breast cancer. The WCRF/AICR report states that no conclusions can be made regarding the role of milk, other dairy products, calcium, or vitamin D and breast cancer risk.

With respect to prostate cancer, epidemiological studies show either a positive or no association with dairy foods, calcium, or vitamin D. Based on epidemiological findings, the WCRF/AICR report concludes that diets high in calcium (>1,500 mg/day) are a "probable" cause of prostate cancer, and there is only a "limited-suggestive" association between dairy food consumption and an increased risk for prostate cancer. Notably, a randomized clinical trial of calcium supplementation and prostate cancer found no increase in prostate cancer and some suggestion of a protective effect.

In addition to calcium and vitamin D, other components in dairy foods may reduce cancer risk. These include conjugated linoleic acid (CLA), butyric acid, sphingolipids, protein and their peptides, and probiotics.

Dietary guidance to prevent cancer includes achieving and maintaining a healthy body weight, being physically active, consuming a healthful diet with an emphasis on foods of plant origin, and limiting consumption of energy-dense foods and alcoholic beverages. Dairy foods are recognized as an important source of nutrients such as calcium and vitamin D, which may have beneficial effects on cancer, particularly colorectal cancer. The WCRF/AICR report does not call for modifications in the 2005 Dietary Guidelines, which recommends three servings of fat-free or low-fat milk, cheese or yogurt a day.



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## INTRODUCTION

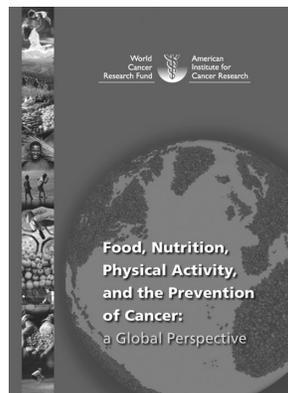
Cancer is the second most common cause of death in the U.S., exceeded only by heart disease (1). Over the past several decades considerable scientific evidence has accumulated indicating that modifications in lifestyle, including diet, can have a major effect on the risk for specific cancers (1-3). Release of the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR)'s second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective* (2), has heightened awareness of the relationship between diet, specific foods, and cancer risk.

Numerous studies have examined the role of dairy foods and dairy food nutrients (e.g., calcium, vitamin D, conjugated linoleic acid, sphingolipids, milk proteins and their peptides) in cancer prevention (3). This Digest reviews some of this research as related to cancers of the colon, breast, and prostate. Also, recent dietary guidelines to prevent cancer are presented.

## DAIRY, DAIRY NUTRIENTS, AND CANCER

**Coloni/Colorectal Cancer.** A variety of studies have investigated a protective role for dairy foods and dairy food nutrients such as calcium and vitamin D against colorectal cancer, the third most common type of cancer in both men and women (1-3). In experimental animal and *in vitro* studies, calcium and/or vitamin D has been shown to reduce markers of increased colon cancer risk (e.g., hyperproliferation of colonic epithelial cells) or tumors induced by carcinogens (3). These types of studies also have suggested plausible mechanisms such as the ability of dietary calcium to bind and inactivate carcinogenic substances such as secondary bile salts and free fatty acids in the gut lumen (3).

Findings from epidemiological studies are generally supportive of a protective effect of calcium, vitamin D, and dairy products against colon or colorectal cancer (2-11). When researchers examined associations between calcium and vitamin D intakes from foods and dietary supplements and colorectal cancer risk in a multi-ethnic



*The World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AICR) has published its Second Expert Report, "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective." This comprehensive report examines the research related to diet, specific foods including dairy foods, and cancer risk and makes recommendations for cancer prevention.*

population of more than 85,000 men and 105,000 women living in Hawaii and Los Angeles, California, they found that calcium, vitamin D, and dairy products were associated with reduced risk for colorectal cancer (4). The highest quintile of total calcium intake (>611 mg/1,000 kcal/day) was associated with a 30% reduced risk of colorectal cancer in men and a 36% reduced risk in women. A reduced risk for colorectal cancer was shown for total (i.e., from diet and supplements) vitamin D intake in men, but not in women. A protective effect of dairy products, a rich source of both calcium and vitamin D, was observed in both men and women (4).

Calcium alone (9) or in combination with vitamin D (10) has been shown to be inversely associated with colorectal cancer or colorectal polyps. With respect to vitamin D, the results of a meta-analysis of five studies exploring serum vitamin D levels and colorectal cancer risk showed that higher vitamin D levels were associated with a 50% lower risk of colorectal cancer (11). The researchers recommend a daily vitamin D<sub>3</sub> intake of 1,000 to 2,000 I.U. a day to reduce the incidence of colorectal cancer (three servings of vitamin D fortified milk provide 300 I.U. of vitamin D) (11).

Several clinical trials in humans support a protective effect of calcium, vitamin D, and/or dairy foods on markers of colon cancer or colon cancer per se (3,12-16). In a randomized, single-blind controlled trial of 70 patients with a history of developing polyps or noncancerous growths in the colon, risk of colon cancer was reduced in those who increased their intake of food sources of calcium (i.e., to bring their calcium intake up to 1,500 mg calcium per day), specifically low-fat dairy foods (12). In a follow-up randomized, cross-over, clinical trial in which the effects of calcium supplements were compared to low-fat dairy foods in 40 adults at risk for colon cancer, both supplemental calcium and dairy foods reduced epithelial cell proliferation indexes from a high to a lower risk pattern (13). Changes in adenomatous tissue in patients receiving calcium plus vitamin D supplements may have reduced polyp formation (14).

A large, blinded, placebo-controlled clinical study involving 930 adults with a history of

colorectal adenomas found that increasing calcium intake by 1,200 mg/day reduced the incidence of recurrent adenomatous polyps by 19% and the total number of tumors by 24% in less than one year (15). A follow-up study found that this beneficial effect persisted for as long as five years after discontinuation of the calcium supplements (16). Increased calcium intake appears to be most protective against advanced colorectal adenomas, which are strongly associated with colorectal cancer (17).

Although findings from epidemiological studies are generally supportive of a protective effect of calcium, vitamin D, and dairy food intake on colon cancer risk, some inconsistencies occur (2,18-20). Some studies in large populations have shown threshold values of 1,000 to 1,400 mg of calcium, above which increased calcium intake does not confer additional benefit on colorectal cancer risk (5,6,20). Other factors such as subjects' compliance to the study regimen, the duration of the study, confounding dietary factors, and imprecise measurement of dietary intake in large population studies may influence findings.

The WCRF/AICR second Expert Report (2) concludes that "milk probably protects against colorectal cancer." This conclusion is based on reasonably consistent evidence from cohort studies supported by strong evidence from dietary calcium studies and evidence for plausible mechanisms (2). The Report graded the strength of evidence in up to five categories: convincing, probable, limited (limited-suggestive and limited-no conclusion), and "substantial effect on risk unlikely" (2).

Additional support for a protective effect of milk and calcium against colorectal cancer is provided by findings from a meta-analysis of more than 26,000 colorectal cancer cases from 60 epidemiological studies (21). Increasing milk intake reduced colon cancer risk by 22%, whereas there was little effect on rectal cancer risk. Comparing the lowest to highest calcium intakes reduced the risk of both colon and rectal cancer by approximately 25 to 45%. Based on a recent study, researchers suggest that following the USDA Food Guide Diet, the DASH (Dietary Approaches to Stop Hypertension) eating plan, or the Mediterranean dietary pattern may

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reduce the risk of colorectal polyps (22). Recommended dairy food intakes for these plans are as follows: at least three servings for the USDA Food Guide, at least two servings for the DASH eating plan, and less than 1.6 servings for the Mediterranean dietary pattern.

**Breast Cancer.** Breast cancer is the most common cancer diagnosed among American women and is second only to lung cancer as a cause of cancer deaths among women (1). Although experimental animal data indicate that dairy food components may reduce the risk of breast cancer, epidemiological studies have yielded inconsistent results (2,3,23-25). A review of 46 case-control and cohort studies and nine case-control studies found no consistent association between a high intake of dairy products as a whole or stratified according to high-fat or low-fat dairy foods, and breast cancer risk (23). A review of prospective studies found no consistent or statistically significant association between various dietary factors including dairy consumption and vitamin D and breast cancer, with the exception of alcohol intake, overweight, and weight gain (25).

Some studies suggest that consumption of dairy foods or calcium may actually protect against breast cancer (26,27). Researchers from the American Cancer Society found that higher intakes of both dietary calcium and low-fat dairy foods were associated with a moderately lower risk of developing breast cancer in a prospective study of more than 68,500 postmenopausal women (26). In this study, women who consumed more than 1,250 mg of dietary calcium a day had a 20% lower risk of postmenopausal breast cancer than those who consumed less than 500 mg/day (26). Also, consumption of at least two servings of dairy foods daily was associated with a 19% lower risk of breast cancer compared to one-half serving or less.

The beneficial effect of calcium and vitamin D, or dairy products on breast cancer risk appears to be greater for premenopausal than postmenopausal women (28-30) and more protective against aggressive or advanced tumors (29). Calcium and vitamin D, either independently or combined, may reduce the risk for breast cancer, at least among premenopausal women, by their effects on

mammographic breast density, a strong risk factor for breast cancer (31,32).

A pooled analysis of observational studies concluded that an intake of 2,000 IU of vitamin D<sub>3</sub> (i.e., the current tolerable upper intake level) and very moderate exposure to sunlight (i.e., about 12 minutes/day) could raise blood vitamin D to a level associated with a 50% reduction in the incidence of breast cancer (33). Although dietary vitamin D may modestly reduce breast cancer risk, the heterogeneity in findings raises many questions regarding the dietary source of vitamin D, menopause status, and timing of vitamin D status before the relationship is well understood (34).

The WCRF/AICR report indicates that no conclusions can be made regarding the role of milk, dairy products, or dairy product nutrients such as calcium and vitamin D and breast cancer risk (both premenopausal and postmenopausal) (2). Well-designed cohort studies and clinical trials are needed to confirm the potential protective effects of dairy foods and dairy food nutrients such as calcium and vitamin D on breast cancer (27).

**Prostate Cancer.** Prostate cancer is the most commonly diagnosed cancer and the second (after lung cancer) leading cause of cancer deaths among men (1). Results of epidemiological studies of dairy foods or dairy food nutrients such as calcium and prostate cancer are inconsistent, with studies showing either a positive (35-39) or no (40-44) association. The Multi-ethnic Cohort Study, an eight-year prospective study of more than 82,000 men found no association between calcium and vitamin D intake and total or advanced cancer risk (43). Similarly, the National Institutes of Health-American Association of Retired Persons Diet and Health Study, a six-year prospective study of more than 290,000 men, found no association between calcium intake and total and nonadvanced prostate cancer (44). Both studies found a weak positive association between fat-free milk and prostate cancer. However, one study showed the association with localized/low-grade prostate cancer (43), whereas the other found the association




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*Scientific findings regarding the role of dairy foods and cancers of the breast and prostate are conflicting.*

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with advanced prostate cancer (44). An explanation for the association between low-fat milk and prostate cancer is undetermined.

Inconsistent findings related to dairy, dairy nutrients, and prostate cancer may be explained by grouping all prostate cancers (i.e., non-advanced and advanced) together and by other variables such as the level of calcium or dairy food intake. The inverse association between calcium/dairy food intake and prostate cancer appears to differ by tumor aggressiveness, with a stronger association observed for advanced or aggressive tumors and total prostate cancer (44-46). Also, an increased risk for prostate cancer is associated with calcium intakes (>1,500 mg/day) exceeding current dietary recommendations (45,47-49).

One proposed mechanism to explain the association between high dietary calcium intake and prostate cancer is that dietary calcium suppresses the production of 1,25-dihydroxyvitamin D (calcitriol) from 25-dihydroxyvitamin D, which may increase cell proliferation in the prostate (50). However, findings from other epidemiological studies of vitamin D and prostate cancer are inconsistent (51). Vitamin D may be more protective against aggressive (advanced-stage) than non-aggressive prostate cancer. Also, the optimal level of vitamin D to confer protection against prostate cancer is unknown (51).

Based on epidemiological studies, the WCRF/AICR Expert Report concludes that diets containing 1,500 mg of calcium or higher (i.e., levels greater than the 1,200 mg calcium/day recommended for men aged 51 and older) are a "probable" cause of prostate cancer, and there is only a "limited-suggestive" association between dairy food consumption and an increased risk for prostate cancer (2). The WCRF/AICR panel members called for more research regarding calcium and/or other dairy foods and prostate cancer (2). Other researchers caution against promoting or avoiding dairy intake to protect against prostate cancer until firm conclusions can be reached (46). Data from several epidemiological

studies published after the WCRF/AICR analysis fail to support the hypothesis that calcium and dairy product intake increases risk of prostate cancer (43,44,46).

In a randomized clinical trial, the incidence of prostate cancer was not increased and a slight non-significant decrease in prostate cancer risk with calcium supplementation was found (52). In this trial, 672 men consuming a baseline dietary calcium intake of approximately 900 mg/day were randomly assigned to receive either 1,200 mg of calcium or a placebo daily for four years and subsequently followed for up to 12 years for development of prostate cancer (52).

**Dairy Food Components and Cancer Risk.** As mentioned above, dairy food components such as calcium and vitamin D may have a protective effect against specific cancers. Interestingly, improving calcium and vitamin D status has been shown to reduce all-cancer risk, according to a four-year, double-blind, randomized, placebo-controlled trial among 1,179 postmenopausal women (53). A recent conference on vitamin D and cancer presented evidence of a biologic mechanism for a role of vitamin D in the prevention of colon, breast, and prostate cancers (54). Prospective epidemiological studies suggest that adequate vitamin D status is associated with reduced risk of colorectal cancer, but the findings regarding total cancer mortality are inconsistent (55,56).

Other components in dairy foods, including conjugated linoleic acid (CLA), butyric acid, sphingolipids, protein and their peptides, and probiotics may contribute to the observed protective effect of dairy foods against cancer (3,24,57,58). Numerous studies, primarily *in vitro* and experimental animal, have shown that CLA (i.e., a mixture of isomers or individual isomers) has an anticarcinogenic effect at various sites including the mammary gland, colon, prostate, and skin (59). Milk, butter, yogurt, and cheese contain considerable amounts of CLA (60). Moreover, 90% of the CLA in dairy foods




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*Promising research suggests that several components of dairy foods – calcium, vitamin D, conjugated linoleic acid (CLA), butyric acid, sphingolipids, protein and their peptides, and probiotics – may have anti-cancer properties.*

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is the biologically active cis-9, trans-11 isomer (60). According to a recent review of individual CLA isomers, for all cancers tested the cis-9, trans-11 isomer reduced the development of cancers in most of the studies with no affect in others (59). Because CLA is a component of fat, higher fat dairy products such as whole milk, cheese, and butter have more CLA than fat-free or reduced-fat milk and other dairy products (60). Milk fat also contains butyric acid, which has been shown to inhibit cancer in *in vitro* and experimental animal studies (24,57,58).

Milk and milk products are very good sources of sphingolipids, a complex group of lipids with biological activity (61). Sphingolipids are present mainly in cell membranes, rather than in fat droplets. As such, there is no correlation between a dairy product's fat content and its sphingolipid content. Although there are no investigations in humans, findings from experimental animal and *in vitro* studies suggest that sphingolipids are potential anticarcinogenic ingredients (61).

Certain milk proteins and their peptides have been proposed to have anticarcinogenic effects (62). Also, probiotics (i.e., live microorganisms that confer health benefits) such as lactic acid bacteria in fermented or culture-containing dairy products (e.g., yogurt) may reduce the risk of some cancers such as those of the colon and breast (63,64).

## CONCLUSION

Although emerging scientific findings support a potentially protective role for milk and milk's nutrients such as calcium and vitamin D in colorectal cancer, findings related to breast and prostate cancer are unclear.

Current guidance to prevent cancer recommends achieving and maintaining a healthy body weight, being physically active, consuming a healthful diet with emphasis on foods of plant origin, and limiting consumption of energy-dense foods and alcoholic beverages (2,65). Dietary guidance to prevent cancer does

not restrict intake of dairy foods. On the contrary, dairy foods are recognized as an important source of nutrients such as calcium and vitamin D, which may have beneficial effects on cancer, particularly colorectal cancer. To prevent colorectal cancer, the American Cancer Society (ACS) recommends that both men and women aim to consume recommended levels of calcium (i.e., 1,000 mg/day for people aged 19 to 50 and 1,200 mg/day for those older than 50 years), primarily through food sources such as low-fat or non-fat dairy products (65). The ACS also encourages adequate intake of vitamin D through a balanced diet, supplementation, and small amounts of skin exposure to ultraviolet radiation.

The WCRF/AICR Expert Report (2) does not call for modifications in the 2005 Dietary Guidelines, which recommends consumption of three servings of fat-free or low-fat milk, cheese, or yogurt a day (66). Also, the WCRF/AICR report makes no public health recommendations regarding the consumption of dairy foods (2). However, the report recommends meeting nutritional needs through diet alone (2). D

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## ACKNOWLEDGMENTS

National Dairy Council® assumes the responsibility for this publication. However, we would like to acknowledge the help and suggestions of the following reviewer in its preparation:

- Peter R. Holt, M.D.  
Director, James E. Olson Colon Cancer Prevention Program  
Institute for Cancer Prevention  
New York, NY

The *Dairy Council Digest*® is written and edited by Lois D. McBean, M.S., R.D.

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